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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/742,785	12/20/2000	William J. Curatolo	PC10755AJTJ	8464

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 03/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/742,785	CURATOLO ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/20/2006; 12/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-15,18-44,47-72,75-92,95-102,104-112,115-122,124-132 and 135-163.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 3-11,19-24,32-40,48-53,60-68,76-81,88-91,96-101,108-111,116-121,128-131,136-141 and 148-150.

Continuation of Disposition of Claims: Claims rejected are 1,2,12-15,18,25-31.41-44,47,54-59,69-72,75,82-87,92,95,102,104-107,112,115,122,124-127,132,135,142-147 and 151-163..

DETAILED ACTION

Examiner acknowledges receipt of amendment, remarks and request for extension of time, all filed 12/07/05; and IDS filed 01/20/06 and 12/09/05. Claims 1-15, 18-44, 47-72, 75-92, 95-102, 104-112, 115-122, 124-132 and 135-163 are pending.

Claim Rejections - 35 USC § 102

1. Claims 1, 2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135 and 142-145 remain rejected under 35 U.S.C. 102(b) as being anticipated by Miyajima et al. (US 4,983,593).

Applicants argue that the amendment to the claims requiring that "when the low solubility drug is basic, the solubility improved form of the drug has an aqueous solubility of at least 2 fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form" excludes Miyajima as art because Miyajima discloses only the hydrochloride form.

2. Applicants' arguments filed 12/07/05 have been fully considered but they are not persuasive.

The Miyajima NZ-105 is not a simple hydrochloride salt as, for example, amitriptyline HCl, rather it is a carboxylate hydrochloride ethanol--- X.HCL.C_2H_5OH form--- with X as the large pyridine derivative, and Miyajima in the background specifically refers to the compound (I) as a solvate (see column 1, lines 7-30 of Miyajima). Secondly, the proviso does not exclude NZ-105 as drug in a pharmaceutically acceptable solubility improved form. There is no factual evidence that the NZ-105 would not have at least 2 fold the solubility of the more soluble of the crystalline hydrochloride salt. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing

that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). No specific drug is identified in or by the claims.

The text of the previous rejection follows below.

3. Miyajima discloses a composition that comprises 5-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)-1,4-dihydro-2,6-dimethyl-4- (3- itrophenyl)-3-pyridine carboxylic acid 2-(phenylmethyl)amino) ethyl ester P-oxide hydrochloride-thanol (NZ-105) and hydroxypropylmethylcellulose acetate succinate ("HPMCAS") and the composition can be mixed with fillers (sugars, e.g. lactose, sucrose, etc., glycitols, e.g. mannitol, sorbitol, xylitol, etc., starches, e.g. corn starch, potato starch, wheat starch, rice starch, etc., crystalline cellulose, inorganic salts, e.g. calcium hydrogen phosphate anhydride, synthetic aluminum silicate) or disintegrants, binders, lubricants or other additives (abstract; column 2, lines 34-40; column 4, lines 16-46; and Examples 1-6). Miyajima's composition also contains urea or surface active agents (column 4, line 49) and is prepared by dissolving NZ-105 and HPMCAS in an organic solvent, removing the solvent by freeze drying, spray drying or vacuum drying (column 3, lines 55-65). NZ-105 is a drug and HPMCAS meets the limitation of the concentration-enhancing polymer since HPMCAS is one of the concentration enhancing polymers recited in the instant claims. Tablets and capsules are orally administered dosage forms,

According to paragraphs [0024], [0025] and [0026] of the published application, "solubility-improved form" is a "form of the drug which has increased solubility relative to the least soluble form of the drug known. Thus, the term implies that a less soluble form of the drug exists and is either known or has been determined, i.e., known, for example, from the scientific or patent literature, or determined by or otherwise known to the investigator. A "solubility-

improved form" may consist of a **highly soluble form of the drug alone**, may be a composition comprising a **highly soluble form of the drug plus inert excipients**, or may be a composition comprising the drug in **a poorly or highly soluble form and one or more excipients which have the effect of increasing the solubility of the drug,** regardless of the length of time for which the solubility is increased. Examples of "solubility-improved forms" include but are not limited to: (1) a crystalline highly soluble form of the drug **such as a salt**; (2) a high-energy crystalline form of the drug; (3) a hydrate or solvate crystalline form of a drug; (4) an amorphous form of a drug (for a drug that may exist as either amorphous or crystalline); (5) a mixture of the drug (amorphous or crystalline) and a solubilizing agent; or (6) a solution of the drug dissolved in an aqueous or organic liquid."

"Alternatively, the term "solubility-improved form" refers to a form of the drug alone or in a composition as is described above that, when delivered to an in vivo environment of use (such as, for example, the gastrointestinal tract of a mammal) or a physiologically relevant in vitro solution (such as phosphate buffered saline or a Model Fasted Duodenal solution described below) provides, or is capable of providing, at least temporarily, a concentration of drug that is at least 1.25-fold the equilibrium concentration of drug in the use environment."

"A solubility-improved form of a drug is one that meets at least one of the above definitions."

While Miyajima does not describe HPMCAS as a concentration-enhancing polymer, the instant claims recite HPMCAS as one of the concentration enhancing polymers. Aqueous solubility of less than mg/ml is a property of the drug. No specific drug is recited in the instant

claims. NZ-105 is a drug that is poorly soluble in water (column 1, lines 37-58). The method claims administer the drug composition. Miyajima also administers the composition.

4. Claims 1, 2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75 and 82-85 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn (US 4,461,759).

Applicants argue that the solubility of Verapamil HCl in water is 83 mg/mL according to the Merck Index, that the solubility of 83 mg/ml is well beyond the aqueous solubility imposed by applicants, that Dunn does not describe a physical mixture because the purpose of Dunn is to provide controlled release dosage form of verapamil HCl that meters out verapamil at a constant rate.

5. Applicants' arguments filed 12/07/05 have been fully considered but they are not persuasive.

While Dunn uses the hydrochloride salt in the examples, it is noted that Dunn states that **verapamil or pharmaceutically acceptable salt** (abstract; column 3, lines 6 and 7) and thus, Dunn specifically contemplates verapamil as well as the pharmaceutically acceptable salt such as the hydrochloride. It is also noted that the claims do not recite any specific solubility except that the claims state a relative solubility. The instant composition comprises ... and the instant claims do not recite a physical mixture and the prior art does not describe a chemical interaction between the drug and the polymer where a covalent or ionic bond is formed. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The rejection follows below.

Dunn discloses a composition that comprises a composition that comprises varapamil and acid retardant cellulose derivative (abstract; column 3, lines 6-15) and when cellulose acetate phthalate is the acid retardant, the drug and the cellulose acetate phthalate and/or bulking or disintegrant agent are granulated (column 4, lines 30-35). Varapamil is poorly soluble in water. See also claims 8 and 9. While Dunn does not describe cellulose acetate phthalate as a concentration-enhancing polymer, the instant claims recite cellulose acetate phthalate as one of the concentration enhancing polymers. Aqueous solubility of less than mg/ml is a property of the drug. No specific drug is recited in the instant claims.

6. Claims 1, 2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 125-127, 132, 135 and 142-145 remain rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al. (US 5,496,561).

Applicants argue that Okada does not disclose physical mixture and that there is no basis to conclude that a physical mixture encompasses any embodiment including the composition of Okada.

7. Applicants' arguments filed 12/07/05 have been fully considered but they are not persuasive. Okada does not disclose a chemical combination of the drug and the polymer where a covalent or ionic bond is formed. The instant composition comprises a drug and concentration enhancing polymer, where the composition is a dispersion and does not exclude the composition of Okada because Okada does not describe the formation of covalent or ionic bond between the drug and the polymer, such a bond formation would not be a physical process. Also there is no claim to a physical composition in the examined claims. The claims are directed to broad subject matter of drug combined with any of the polymers recited. The rejection is reproduced below.

Okada discloses a controlled release pharmaceutical composition comprising crystalline form of a drug (column 3, line 32); polymer such as hydroxypropylmethylcellulose acetate succinate, hydoxypropylmethylcellulose phthalate, cellulose acetate phthalate and carboxymethylethyl cellulose (column 3, lines 36-39, column 4, lines 20-25); plasticizers such as triethyl citrate, triacetin, polyethylene glycol, castor oil, polysorbitan monooleate, glycerine fatty acid ester (column 5, lines 5-8).

The instant application claims a composition that comprises a drug in a pharmaceutically acceptable solubility-improved form and a concentration-enhancing polymer is a salt and several examples of drugs that are suitable in the instant invention are listed in the specification (page 30, line 31 to page 31 line 5, page 35, line 13 to page 36 line 26 and page 26, line 30 to page 29 line 18). In the instant application, the recitation that the composition achieves a maximum equilibrium concentration of at least 1.25 fold of a drug ... is a property of the drug composition and property of a composition is not separable from the composition; and thus the composition of the prior art would inherently achieve said equilibrium concentration relative to the drug.

Instant claims 25-28, 30, 54-57 and 82 recite the property of the composition and the teaching of Okada meets the limitations of said claims; diclofenac, which is one of the drugs disclosed in Okada has analgesic, anti-inflammatory and antipyretic activities; and thus Okada meets the limitation of instant claim 29. The method of the instant claims administers the drug and the concentration-enhancing polymer and the prior art teaches administering the composition to a patient/subject in need thereof.

Applicants combined the arguments against the anticipatory rejection by Bymaster and the obviousness rejection over Bymaster. Therefore, a combined response is given in support of the rejections over Bymaster

8. Claims 1, 30, 58, 86, 126 and 156-161 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bymaster et al. (US 6,147,072).

Claim Rejections - 35 USC § 103

9. Claims 146, 147, 151-155, 162 and 163 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bymaster et al. (US 6,147,072).

Applicants argue that Bymaster does not disclose physically mixing solubility-improved drug with any of the polymers recited by the instant claims and that there is no disclosure in Bymaster of a physical mixture between the drug and applicants polymers. Regarding the rejection under 35 USC 103, applicants state that Bymaster does not suggest the instant composition, does not suggest a reasonable expectation of success to make applicants' claimed composition and there Bymaster is insufficient to support the legal basis obviousness rejection

10. Applicants' arguments filed 12/07/05 have been fully considered but they are not persuasive.

Bymaster does describe chemical interaction between the drug and the polymer and the claims do not recite physical interaction or exclude chemical interaction. Bymaster does not disclose the formation of covalent or ionic bonds between the drug and the polymer that would otherwise provide a basis for interaction that is not physical. The claims recite combining concentration enhancing polymer with solubility-improved form. In Bymaster, the drug and the polymer are combined to form a composition and the prior art meets the limitation of the broad combination.

Regarding the rejection under 35 USC 103, the difference between the instant claims and Bymaster was specifically stated as being difference in the size of the particles and thus the proper analysis for the rejection was made. Applicants provided no factual evidence that the recited

particle sizes provide unusual and unexpected results to the composition. In the rejection under 35 USC 102, it is noted that "when the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The rejections are repeated below;

35 USC 102:

Bymaster discloses treating psychosis, acute mania, mild anxiety states or depression by administering to a patient in need thereof a composition that comprises a first component drug selected form olanzapine, clozapine, risperidone, sertindole, quetiapine and ziprasidone, and a second component (abstract; column 1, lines 42-46; column 2, line 9-51; and claim 2), and the composition is formulated as tablets, chewable tablets, capsules, solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions (column 10, lines 8-12) and polymers such as hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate are associated with the drug (column 10, lines 61-67).

35 USC 103:

Bymaster is discussed above. The difference between Bymaster and the instant claims is that Bymaster does not disclose the drug-polymer particles range in sizes of from about 10 to about 1000 nanometers. However, there is no demonstration that particles having sizes of from about 10 to 1000 nanometers provides unusual results. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition of Bymaster where the drug and the polymer are associated with the expectation of delivering effective amounts of the drugs to effectively treat the targeted condition.

The below rejection is repeated and it is noted that applicants have not traversed the below rejection.

11. Claims 87, 92, 95, 102, 105-107, 112, 115, 122, 124-127, 132, 135 and 142-145 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn (US 4,461,759).

Dunn is discussed above. Dunn discloses a composition where the drug verapamil and cellulose acetate phthalate are granulated. Dunn does not discuss administering the verapamil composition to a subject in need thereof. Verapamil is a cardiovascular drug and the drug composition has to be administered in order for it to provide cardiovascular positive effect in a subject. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the cardiovascular composition comprising verapamil. One having ordinary skill in the art would have been motivated to administer the verapamil formulation to a subject in need thereof with the expectation of treating cardiovascular problems such as irregular heartbeats (arrhythmias) and high blood pressure.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 3:30 p.m. (Monday to Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-272-0594.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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